REMARKS

In response to the action mailed September 24, 2001 ("Office Action") in the parent application U.S. Appln. No. 09/812,940, Applicants submit the following remarks.

Claims 1, 20, 21, 22 and 43 have been amended. Support for the amendments can be found throughout the specification. The specification has also been amended to correct typographical errors. No new matter has been added.

Information Disclosure Statement

Applicants thank the Examiner for noting that he did not receive copies of the foreign patents and publications listed on the PTO Forms 1449 filed July 23, 2001. Page 2 of the Office Action. Copies of these references were provided with the Information Disclosure Statement filed July 23, 2001. A copy of the date-stamped postcard confirming filing of 140 references is attached.

Applicants attach herewith copies of the foreign patents and publications, along with copies of all previously filed PTO Forms 1449 for consideration by the Examiner.

Election of Species

This amendment is being filed as part of a continuation application. Applicants withdraw the previous election and elect 7,7-diphenyl-2,4,6-heptatrieneoic acid for examination. See MPEP 819. Claims 1-5, 7, 8, 12, 13, 16, 17, 22, 25, and 26 read on the newly elected species.

Specification

The specification has been amended to address objections raised by the Examiner.[1] Pages 2-3 of the Office Action.

The Examiner has also noted that "incorporation of essential material in the specification (page 15, lines 23-24) by reference to a foreign application or patent, or to a publication is improper. Application is required to amend to the disclosure to include the material incorporated by reference." Page 3 of the Office Action. MPEP 608.01(p) defines "essential material" as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describes the best mode." MPEP 608.01(p) further explains that "[n]onessential subject matter is subject matter referred

1 Please note that the typographical errors noted by the Examiner at page 3, line 6 and page 12, line 6 were at page 3, line 26 and page 12, line 11, respectively.

to for purposes of indicating the background of the invention or illustrating the state of the art. Applicants believe that the references incorporated by reference indicates the background of the invention or illustrates the state of the art, and, therefore, is nonessential material with respect to the claimed invention. Thus, Applicants do not believe the specification requires the requested amendment. If the Examiner believes otherwise and has particular instances where he believes essential material has been incorporated by reference, Applicants would be willing to amend the specification accordingly.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the objections.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-5, 7, 8, 12, 13, 16, 17, 20-22, 25 and 26 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Pages 3-4 of the Office Action.

Claims 1 and 22

With respect to claims 1 and 22, the Examiner contends that the phrase "that when L contains two or more double bonds, the double bonds are not adjacent to one another" is indefinite "because it is unclear what Applicant intends by the word 'adjacent' since both allenes and conjugated di- or polyenes can be considered to have 'adjacent' double bonds."[2] Page 4 of the Office Action. Webster's II New Riverside University Dictionary, 1984, defines adjacent as "next to" (see Tab A). As recognized by the Examiner, this meaning includes "allene". Double bonds in conjugated di- or polyenes do not need to be described as being "adjacent" -- the double bonds are conjugated. Indeed, the claims include compounds containing conjugated double bonds, such as, for example, claim 20. Thus, meaning of the word "adjacent" in claims 1 and 22 is clear.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 20 and 21

Claims 20 and 21 were rejected as being indefinite for a reason related to the rejection of claims 1 and 22. Specifically, the Examiner observes that "Claims 20 and 21 depend upon Claim 1 but list species all of which contain adjacent, conjugated double bonds." Page 4 of the Office Action. Claims 20 and 21 depend from independent claim 1. As explained with

2 It is believed based on the rejection that the Examiner's reference to "Claims 1 and 10" at page 4, line 3, is intended to refer to "Claims 1 and 22." Applicants respectfully request clarification if their belief is incorrect.

respect to claims 1 and 22, "adjacent" means "next to." Thus, the phrase in claim 1 and refers to allenes, not conjugated double bonds. Accordingly, claims 20 and 21 are definite.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 25 and 26

Claim 25 has been rejected as being indefinite because it "recites the limitation 'containing only double bonds' in line 2 but depends upon Claim 22 which requires a triple bond." Page 4 of the Office Action. Applicants respectfully disagree.

Claim 22 states that "L is a straight C_{3-12} hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond." Thus, L can contain: (1) at least one double bond; (2) at least one triple bond; or (3) at least one double bond and one triple bond. Thus, claim 22 does not "require a triple bond," as asserted by the Examiner. Claim 25 then states that "L is an unsaturated C_{4-8} hydrocarbon chain containing only double bonds in trans configuration." In claim 25, L contains at least one double bond, and is one of the L groups described in claim 22. Accordingly, claims 25 and 26 are definite.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 43

Claim 43 has been rejected as being indefinite. Page 4 of the Office Action. Claim 43 has been amended to provide proper antecedent basis. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §102(b)

Claims 1-5, 7, 8, 12, 13, 16, 17, 20-22, 25 and 26 were rejected as being anticipated by Patel *et al.*, J. Org. Chem. 43(26):5018-5020 (1978) ("Patel"). Amended independent claims 1 and 22 do not read on 7-phenyl-2,4,6-heptatrieneoic acid. Patel does not describe compounds of amended independent claims 1 and 22. Accordingly, independent claims 1 and 22, and claims depending therefrom, are not anticipated by Patel. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

The following paragraph was inserted at page 1, line 2:

--This application is a continuation of U.S. Patent Application Serial No. 09/812,940, filed on March 27, 2001, the entire contents of which are hereby incorporated by reference.--

Paragraph beginning at page 1, line 13 has been amended as follows:

--Regulation of gene expression through the inhibition of the nuclear enzyme histone deacetylase (HDAC) is one of several possible regulatory mechanisms whereby chromatin activity can be affected. The dynamic homeostasis of the nuclear acetylation of histones can be regulated by the opposing activity of the enzymes histone acetyl transferase (HAT) and histone deacetylase (HDAC). Transcriptionally silent chromatin can be characterized by nucleosomes with low levels of acetylated histones. Acetylation of histones reduces its positive charge, thereby expanding the structure of the nucleosome and facilitating the interaction of transcription factors to the DNA. Removal **of** the acetyl group restores the positive charge condensing the structure of the nucleosome. Acetylation of histone-DNA activates transcription of DNA's message, an enhancement of gene expression. Histone deacetylase can reverse the process and can serve to repress gene expression. See, for example, Grunstein, *Nature* 389, 349-352 (1997); Pazin et al., *Cell* 89, 325-328 (1997); Wade et al., *Trends Biochem. Sci.* 22, 128-132 (1997); and Wolffe, *Science* 272, 371-372 (1996).--

Paragraph beginning at page 3, line 20 has been amended as follows:

--In another aspect, carboxylic acid-containing compounds have a structure of formula (I), *supra*. A is a heteroaryl optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, or amino. Each of X^1 and X^2, independently, is O or S, and each of Y^1 and Y^2, independently, is $-CH_2-$, -O-, -S-, $-N(R^a)-$, $-N(R^a)-C(O)-O-$, $-O-C(O)-N(R^a)-$, $-N(R^a)-C(O)-N(R^b)-$, -O-C(O)-O-, or a bond; each of R^a and R^b, independently, being hydrogen, alkyl, hydroxylalkyl, or haloalkyl. L is a straight C_{3-12} hydrocarbon chain optionally containing at least one double bond, at least one **[a]** triple bond, or at least one

double bond and one triple bond. The hydrocarbon chain is optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, or amino, and further optionally interrupted by -O- or -N(R^c)-, where R^c is hydrogen, alkyl, hydroxylalkyl, or haloalkyl.--

Paragraph beginning at page 12, line 10 has been amended as follows:

--The activities of a compound described herein can be evaluated by methods known in the art, e.g., MTT (3-[4,5-**[dimehtythiazol]**<u>**dimethylthiazol**</u>-2-yl]-2,5-diphenyltetrazolium bromide) assay, clonogenic assay, ATP assay, or Extreme Drug Resistance (EDR) assay. See Freuhauf, J.P. and Manetta, A., *Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer* 19, 39 – 52 (1994). The EDR assay, in particular, is useful for evaluating the antitumor and antiproliferative activity of a compound of this invention (see Example 28 below). Cells are treated for four days with compound of the invention. Both untreated and treated cells are pulsed with tritiated thymidine for 24 hours. Radioactivity of each type of cells is then measured and compared. The results are then plotted to generate drug response curves, which allow IC_{50} values (the concentration of a compound required to inhibit 50% of the population of the treated cells) to be determined.--

Paragraph beginning at page 12, line 25 has been amended as follows:

--Histones are isolated from cells after incubation for periods of 2 and 24 hours. The cells are centrifuged for 5 minutes at 2000 rpm in the Sorvall SS34 rotor and washed once with phosphate buffered saline. The pellets are suspended in 10 ml lysis buffer (10 mM Tris, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM magnesium chloride, 8.6% sucrose, pH 6.5) and homogenized with six strokes of a Teflon pestle. The solution is centrifuged and the pellet washed once with 5 ml of the lysis buffer and once with 5 ml 10 mM Tris, 13 mM EDTA, pH 7.4. The pellets are extracted with 2 x 1 mL 0.25N HCl. Histones are precipitated from the combined extracts by the addition of 20 mL acetone and refrigeration overnight. The histones are pelleted by centrifuging at 5000 rpm for 20 minutes in the Sorvall SS34 rotor. The pellets are washed once with 5 mL acetone and protein concentration **[are]** <u>**is**</u> quantitated by the Bradford procedure.--

Paragraph beginning at page 13, line 5 has been amended as follows:

--Separation of acetylated histones is usually performed with an acetic acid-urea polyacrylamide gel electrophoresis procedure. Resolution of acetylated H4 histones is achieved with **[6,25N]** **6.25N** urea and no detergent as originally described by Panyim and Chalkley, *Arch. Biochem. Biophys.* 130, 337-346 (1969). 25 μg total histones are applied to a slab gel which is run at 20 ma. The run is continued for a further two hours after the Pyronon Y tracking dye has run off the gel. The gel is stained with Coomassie Blue R. The most rapidly migrating protein band is the unacetylated H4 histone followed by bands with 1,2,3 and 4 acetyl groups which can be quantitated by densitometry. The procedure for densitometry involves digital recording using the Alpha Imager 2000, enlargement of the image using the PHOTOSHOP program (Adobe Corp.) on a MACINTOSH computer (Apple Corp.), creation of a hard copy using a laser printer and densitometry by reflectance using the Shimadzu CS9000U densitometer. The percentage of H4 histone in the various acetylated states is expressed as a percentage of the total H4 histone.--

Paragraph beginning at page 32, line 21 has been amended as follows:

--The PC3 cell line was maintained in RPMI supplemented with 10% fetal calf serum and antibiotics. Cells were suspended in 0.12% soft agar in complete medium and plated (2,000 cells per well) in different drug concentrations onto a 0.4% agarose underlayer in 24-well plates. Plating **[calls]** **cells** on agarose underlayers supports the proliferation only of the transformed cells, ensuring that the growth signal stems from the malignant component of the tumor.--

Paragraph beginning at page 37, line 24 has been amended as follows:

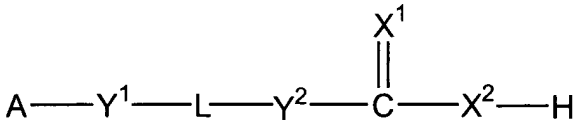
--Cells were treated with test compounds and CFTR immunoprecipitated as described in Bradbury et al., *Am. J. Physiol.* 276, L659 - 668 (1999). Briefly, treated cells were lysed in buffer containing 1% TRITON X-100 and various protease inhibitors. Soluble material was immunoprecipitated using both R domain and C-terminal monoclonal antibodies. Immunoprecipitated CFTR was then subject to *in vitro* phosphorylation using camp-dependent PKA catalytic subunit and [γ-32P]ATP, followed by resolution on SDS-PAGE gels. After fixation, the gels were dried and processed for autoradiography and phosphor

image analysis. Quantitation of B and C bands **was performed** on a BioRad personal fix image analysis station.--

In the claims:

Claims 1, 20-22 and 43 have been amended as follows:

1. (Amended) A compound of formula (I):



(I)

wherein

A is a cyclic moiety selected from the group consisting of C_{3-14} cycloalkyl, 3-14 membered heterocycloalkyl, C_{4-14} cycloalkenyl, 3-14 membered heterocycloalkenyl, aryl, **[or]** **and** heteroaryl; the cyclic moiety being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylsulfonylamino, aminosulfonyl, or alkylsulfonyl;

each of X^1 and X^2, independently, is O or S;

each of Y^1 and Y^2, independently, is $-CH_2-$, -O-, -S-, $-N(R^a)-$, $-N(R^a)-C(O)-O-$, $-O-C(O)-N(R^a)-$, $-N(R^a)-C(O)-N(R^b)-$, -O-C(O)-O-, or a bond; each of R^a and R^b, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl;

L is a straight C_{3-12} hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl, halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, $-N(R^c)-$, $-N(R^c)-C(O)-O-$, $-O-C(O)-N(R^c)-$, $-N(R^c)-C(O)-N(R^d)-$, or -O-C(O)-O-; each of R^c and R^d, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl; provided that when L contains two or more double bonds, the double bonds are not adjacent to each other**; that when L contains three double bonds, said hydrocarbon chain is substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl, halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered**

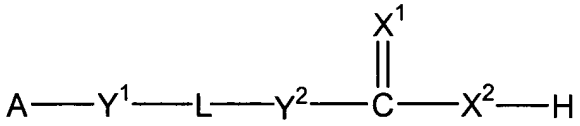
heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl; and further provided that when L contains less than 6 carbon atoms in the hydrocarbon chain **and A is C_{1-4} alkyl phenyl or unsubstituted phenyl**, Y^1 is not a bond;

or a salt thereof.

20. (Amended) The compound of claim 1, said compound being 4-chloro-5-phenyl-2,4-pentadienoic acid, 5-(4-dimethylaminophenyl)-2,4-pentadienoic acid, 5-(2-furyl)-2,4-pentadienoic acid, 5-phenyl-2-en-4-yn-pentanoic acid, **[7-phenyl-2,4,6-heptatrienoic acid,]** or 8-phenyl-3,5,7-octatrienoic acid.

21. (Amended) The compound of claim 1, said compound being **[7-phenyl-2,4,6-heptatrienoic acid or]** 8-phenyl-3,5,7-octatrienoic acid.

22. (Amended) A compound of formula (I):



(I)

wherein

A is a cyclic moiety selected from the group consisting of aryl **[or]** **and** heteroaryl; the cyclic moiety being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, or amino;

each of X^1 and X^2, independently, is O or S;

each of Y^1 and Y^2, independently, is $-CH_2-$, -O-, -S-, $-N(R^a)-$, $-N(R^a)-C(O)-O-$, $-O-C(O)-N(R^a)-$, $-N(R^a)-C(O)-N(R^b)-$, -O-C(O)-O-, or a bond; each of R^a and R^b, independently, being hydrogen, alkyl, hydroxylalkyl, or haloalkyl;

L is a straight C_{3-12} hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, or amino, and further optionally interrupted by -O- or $-N(R^c)-$, where R^c is hydrogen,

alkyl, hydroxylalkyl, or haloalkyl; provided that when L contains two or more double bonds, the double bonds are not adjacent to each other**; that when L contains three double bonds, said hydrocarbon chain is substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl, halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl**; and further provided that when L contains less than 6 carbon atoms in the hydrocarbon chain **and A is C_{1-4} alkyl phenyl or unsubstituted phenyl**, Y^1 is not a bond;

or a salt thereof.

43. (Amended) The compound of claim 40, wherein L is an unsaturated C_{4-8} hydrocarbon chain containing at least one double bond in trans configuration **[and no triple bond]**, said unsaturated hydrocarbon chain being optionally substituted with C_{1-2} alkyl, C_{1-2} alkoxy, hydroxyl, $-NH_2$, $-NH(C_{1-2}$ alkyl), or $-N(C_{1-2}$ alkyl)$_2$.